(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 122 036 B2**

(12) **NEW EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of the new patent specification: **02.11.94**

(21) Application number: **84301546.2**

(22) Date of filing: **08.03.84**

(51) Int. Cl.5: **A61K 37/02**, A61K 37/24, A61K 37/26, A61K 37/30, A61K 39/00, A61K 39/10, A61K 39/145, A61K 9/14, A61K 9/72, A61K 37/66

(54) **Powdery pharmaceutical composition for nasal administration.**

(30) Priority: **09.03.83 JP 37244/83**

(43) Date of publication of application:
17.10.84 Bulletin 84/42

(45) Publication of the grant of the patent:
08.02.89 Bulletin 89/06

(45) Mention of the opposition decision:
02.11.94 Bulletin 94/44

(84) Designated Contracting States:
CH DE FR GB IT LI SE

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EP 0 122 036 B2

(56) References cited:

EP-A- 0 023 359	AT-B- 329 743
AT-B- 330 962	AT-E- 212
DE-A- 2 229 981	DE-A- 2 535 258
DE-A- 2 726 837	DE-B- 1 178 975
FR-M- 2 530	GB-A- 1 018 125
GB-A- 1 183 506	GB-A- 1 236 707
GB-A- 1 461 188	GB-A- 1 527 605
GB-A- 2 016 015	GB-A- 2 041 220
JP-B-62 037 016	US-A- 3 155 573
US-A- 3 632 743	US-A- 4 226 848
US-A- 4 294 829	US-A- 4 349 530

DIABETES, vol. 27, no. 3, March 1978 SHINICHRO HIRAI et al. "Nasal Absorption of Insulin in Dogs", pages 296-299

Journal of Controlled Release, 1 (1984), pages 15-22

Biopharm, April 1988, pages 30-37

Instructionf for use of "Intal nasal" of Fisons Arzneimittel GmbH, Köln, DE; 1988

Instructions for use of "Intal" of Fisons Arzneimittel GmbH, Köln, DE; 1989

Hiral et al., Int. J.Pharm. 7 (1981) 317-325

Hirai et al., Int.J.Pharm. 9 (1981) 165-172

Extra Pharmacopoela , Martindale, 25th Ed., page 926, 927, 938, 1373

J.Pharm. Exp. Ther. 211, pp. 663-667, 1979

Int. J.Appl. Rad. a. Isotopes, 19, 550-552, 1968

Remington's Pharmaceutical Sciences, 15th Edition, 1975, (page 1575)

Controlled Release TEchnology-Pharmaceutical Applications, 1987, chapter 15.

Pharmacy International October 1983, pages 260-262

Bio Engineering News, Vol. 10, No. 51, December 1989

Rote Liste 1982, Editio Cantor, Aulendorf/Württ, DE with Enclosure No. 9c. Annex 4

Rote Liste 1976, Editio Cantor, Aulendorf/Württ., DE

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Leaflet "Verla-Krankenpflegeartikel", pages 60,61, 115	
Leaflet, Glaxo GmbH, "Beconase"(R) Dosier-Spray	
Leaflet, Sandoz, AG, "Syntocinon(R) Spray	
Leaflet, Sandoz AG, "Vasopressin-Sandoz"	
Arch.Intern.Med./Vol. 131, Jan. 1973, pages 60-73	
Health Physics Pergamon Press 1966, Vol. 12, pages 173-207	
Harris et al (1980) J.Pharm. Sci. 69 (11) 1271	

Description

This invention relates to a powdery pharmaceutical composition adepted for nasal administration. More specifically, this invention relates to a powdery composition adepted for nasal administration which comprises a physiologically active polypeptide or its derivative, such as calcitonin or insulin, and a water-absorbing and water-insoluble base selected from celluloses, starches and cross-linked vinyl polymers and which allows said polypeptide or its derivative to be effectively absorbed through the nasal mucosa when nasally administered.

Because of the fact that peptide hormones such as insulin and calcitonin have a high molecular weight and that they are readily decomposed by proteolytic enzymes, such as pepsin, trypsin and chymotrypsin, the peptide hormones are not absorbed sufficiently to display a pharmacological effect efficaciously and accordingly they have been administered by parenteral injection.

However, since the administration by injection causes pain, various attempts to develop alternative methods of administration have been made. For example, there is a method of intrarectal administration of a suppository prepared by use of such salicylic acid derivatives as sodium salicylate, 3-methoxy sodium salicylate, and 5-methoxysalicylic acid as an absorption aid (J. Pharmacol., 33, 334, (1981)). Besides this method, a method of intrabronchial administration (Diabetes, 20, 552, (1971)) and a method of eye-dropping administration (Diabetes Society's Epitomes, 237, (1974)) have been studied.

There are, however, drawbacks to all of these methods in that they require much larger doses than injection and that their absorption is varied and accordingly any of them have hardly been put to practical use as yet.

On the other hand, there is known a method of nasal administration of an acidic aqueous solution of insulin, whereas such a surface active agent as sodium glycocholate is used as an absorption aid, as an attempt to develop a method of intranasal administration (Diabetes, 27, 296, (1978)).

However, this method may not be regarded as an expedient means, since the preparation is prepared in the form of a liquid, often causing the drug to flow out of the nasal cavity upon its administration into the nose and the use of a surface active agent in its preparation also causes inconvenience.

As a powdery pharmaceutical composition for nasal administration, US-A-4,294,829 discloses a pharmaceutical preparation comprising a lower alkyl ether of cellulose and a drug. This pharmaceutical composition is characterized in that its lower alkyl ether of cellulose absorbs moisture on the nasal mucous membrane, and takes the form of a viscous liquid to slowly flow over the nasal mucosa and release the drug slowly. Since a composition of this type takes the form of a viscous liquid in the nasal cavity, a drug with a high molecular weight tends to stay within the lower alkyl ether of cellulose and becomes difficult to release from the composition. The composition of this type should, therefore, still undergo a significant improvement if it is to use such a drug with a high molecular weight as calcitonin or insulin. DE-A-2 535 258 discloses a pharmaceutical composition for use in a mouth inhaler. The composition comprises soft pellets having a size from 10 to 1000 µm which breaks down on inhalation to particles having a size of less than 10 µm so that the particles can lodge in the lungs.

One of the objects of this invention is to provide a powdery pharmaceutical composition for nasal administration.

Another object of this invention is to provide a powdery pharmaceutical composition for nasal administration aimed at application of a physiologically active polypeptide or its derivative.

A further object of this invention is to provide a powdery pharmaceutical composition for nasal administration which allows a physiologically active polypeptide or its derivative to be absorbed efficiently through the nasal mucosa without the use of an absorption aid.

Still another object of this invention is to provide a powdery pharmaceutical composition for nasal administration which especially allows polypeptides, such as insulin and calcitonin, to be absorbed efficiently through the nasal mucosa without the use of an absorption aid.

It is yet another object of this invention to provide a powdery pharmaceutical composition for nasal administration which allows a physiologically active polypeptide or its derivative to be absorbed efficiently through the nasal mucosa and which also has a sustained release effect.

It is still another object of this invention to provide a powdery pharmaceutical composition for nasal administration having such a proper particle diameter as to make it possible to be administered efficiently in the nasal cavity when intranasally sprayed.

Other objects and advantages of this invention will become apparent from the following description.

According to this invention, these objects and advantages are achieved by a powdery pharmaceutical composition adepted for nasal administration which comprises: (i) a physiologically active polypeptide or its derivative; (ii) a water-absorbing and water-insoluble base selected from celluloses, starches and cross-

linked vinyl polymers and (iii) optionally a water-absorbing and water-soluble base, said water-absorbing and water-soluble base being present in an amount of 0.1 to 60 wt%, against the water-absorbing and water-insoluble base; wherein at least 90 wt. % of the particles of said composition have an effective diameter ranging from 10 to 250 μm and wherein said particles do not disintegrate on spraying, provided that the composition does not comprise a mixture of bacitracin and starch.

In the accompanying drawings:

Fig. 1 shows the decrease (%) of plasma glucose levels after the nasal administration of a composition of this invention in which insulin is used as the polypeptide; and

Fig. 2 shows the serum insulin levels after the nasal administration of a composition of this invention in which insulin is used.

As shown in Fig. 1 and Fig. 2, the powdery pharmaceutical composition for nasal administration is a composition which allows a polypeptide such as insulin to be absorbed at a satisfactorily high efficiency.

In this invention, the objective drug is a physiologically active polypeptide or its derivative. As the polypeptide or its derivative, a polypeptide or its derivative with a molecular weight ranging from 1,000 to 300,000 are desirable in view of the fact that they are easily absorbed through the nasal mucous membrane. Especially those having a molecular weight ranging from 1,000 to 150,000 are more desirable.

Desirable physiologically active polypeptides or their derivatives are exemplified in the following. For instance, such peptide hormones as insulin, angiotensin, vasopressin, desmopressin, felypressin, protirelin, luteinizing hormone releasing hormone, corticotropin, prolactin, somatropin, thyrotropin, luteinizing hormone, calcitonin, kallikrein, parathryin, glucagon, oxytocin, gastrin, secretin, serum gonadotrophin, growth hormone, erythropoietin, urogastrone and renin; such physiologically active proteins as interferon, interleukin, transferrin, histaglobulin, macrocortine and blood coagulation factor VIII; such enzyme proteins as lysozyme and urokinase; such vaccines as acellular and cellular pertussis vaccine, diphtheria vaccine, tetanus vaccine, and influenza vaccine; and such toxoids as diphtheria toxoid, tetanus toxoid and toxoids of lymphocytosis promoting factor, and filamentors hemagglutinin (those are contained in acellular pertussis vaccine developed recently in Japan) may be mentioned. Of these polypeptides or their derivatives mentioned above, peptide hormones, physiologically active proteins and vaccines are desirable, and peptide hormones are especially more desirable. Among these peptide hormones, calcitonin, insulin, luteinizing hormone releasing hormone, desmopressin, vasopressin and oxytocin are particularly desirable and calcitonin and insulin are more particularly desirable. Among physiologically active proteins, interferon is particularly desirable, and among vaccines, influenza vaccine and pertussis vaccine are particularly desirable.

For the preparation of powdery pharmaceutical compositions for nasal administration, the physiologically active polypeptide or its derivative is preferred to be one in the form of a powder. The physiologically active polypeptide or its derivative should desirably be water-soluble in view of the fact it is to be absorbed through the nasal mucous membrane. Here, "water-soluble" means that the polypeptide or its derivative is soluble on the human nasal mucous membrane or in a similar environment, or more concretely, it is soluble in an aqueous solution at pH around 7.4 at a temperature of about 36 °C to 37 °C.

In case where polypeptides which are water-insoluble or hardly soluble in water are to be used, it is accordingly advisable, for instance, to adjust their pH, dissolve in water, and freeze-dry, thus making them water-soluble and in the form of powder.

Those polypeptides which are not in the form of powder should desirably be freeze-dried into powder before use.

The aforementioned polypeptide or its derivative can be used in combination with human serum albumin, mannitol, sorbitol, aminoacetic acid, amino acid, sodium chloride or phospholipid for the purpose of stabilization, or for the dual purpose of stabilizing and bulking.

In the preparation of powdery pharmaceutical compositions for nasal administration according to the present invention, a base having a duplicity of properties of being water-absorbing and water-insoluble is used. By the terms of water-absorbing and water-insoluble, it is meant that the base has the double properties of being water-absorbing and water-insoluble on the human nasal mucous membrane or in a similar environment, or more concretely, it is water-absorbing and water-insoluble at pH around 7.4 and at a temperature of 36 °C to 37 °C or thereabout.

Because of the use of a water-absorbing and water-insoluble base, the pharmaceutical compositions of this invention are able to absorb the moisture on the nasal mucous membrane upon its administration into the nasal cavity, thus making each particle, which is not in the state of a viscous fluid and does not flow away immediately but diffuses moderately, stay at the site on the nasal mucosa where it adhered and allows the polypeptide or its derivative with a high molecular weight to come into thorough contact with the nasal mucosa, through which they are absorbed at a high efficiency. In this invention, the selection of such

a base as mentioned above for use as the base of a polypeptide or its derivative preparation for nasal application has made it possible to make the polypeptide or its derivative be absorbed effectively and let it display its pharmacological efficacy sufficiently without the use of an absorption aid.

The water-absorbing and water-insoluble bases which are to be used in this invention should be distinguished from those lower alkyl ethers of cellulose, or more particularly such lower alkyl ethers of cellulose as hydroxypropyl cellulose which dissolve into a viscous fluid on the nasal mucous membrane. As the desirable examples of the water-absorbing and water-insoluble base, the following ones may be mentioned.

They include, for instance, water-absorbing and water-insoluble celluloses such as crystalline cellulose, cellulose, α-cellulose, and cross-linked sodium carboxymethyl cellulose; water-absorbing and water-insoluble starches such as hydroxypropyl starch, carboxymethyl starch, cross-linked starch, amylose, amylopectin and pectin; and cross-linked vinyl polymers such as cross-linked polyvinyl pyrrolidone, cross-linked carboxyvinyl polymer or its salt, cross-linked polyvinyl alcohol and polyhydroxyethylmethacrylate. Of these mentioned above, water-absorbing and water-insoluble celluloses and cross-linked vinyl polymer are desirable, water-absorbing and water-insoluble celluloses are more desirable and crystalline cellulose is especially desirable. Among cross-linked vinyl polymers, cross-linked polyvinylpyrrolidone and cross-linked carboxy vinyl polymer or its salt are desirable.

Since the quantity of a water-absorbing and water-insoluble base to be used varies depending upon the polypeptide or its derivative to be used, it cannot be defined indiscriminately; however, it is desirable in general to use it in appreciable amount of more than 10 times the weight of the polypeptide or its derivative especially more than 15 times, furthermore more than 20 times.

In preparing a pharmaceutical composition of this invention, said water-absorbing and water-soluble base may be used in combination with a water-absorbing and water-insoluble base. The combined use of a water-absorbing and water-soluble base adds some degree of solubility to a water-absorbing and water-insoluble base to produce the following effect. When the pharmaceutical composition is intranasally administered, the particles which comprise a water-absorbing and water-insoluble base and a polypeptide or its derivative are dispersed over the nasal mucous membrane, and the water-absorbing and water-soluble base is dissolved into the state of a viscous fluid, which gives some degree of viscosity and flowage to the whole base of this invention, thus allowing the polypeptide or its derivative to be absorbed slowly, which is known as a sustained release effect.

The water-absorbing and water-soluble base may be used by simply mixing it with the water-absorbing and water-insoluble base or by mixing it with the polypeptide or its derivative at the time of their freeze-drying. In the case where the water-absorbing and water-soluble base is freeze-dried together with the polypeptide or its derivative, the mixture assumes a state in which particles of the polypeptide or its derivative are dispersed among particles of the water-absorbing and water-soluble base and the final product of pharmaceutical composition comes to have much more sustained relese effect.

As the water-absorbing and water-soluble base to be used in this invention, there are, for instance, polyacrylates such as sodium polyacrylate, potassium polyacrylate and ammonium polyacrylate; lower alkyl ethers of cellulose such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose; polvyinyl pyrrolidone; amylose; polyethyleneglycol; and pullulan. Of those mentioned above, polyacrylates such as sodium polyacrylate; lower alkyl ethers of cellulose such as methyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose; polyethyleneglycol; and polyvinyl pyrrolidone are especially desirable. The quantity of water-absorbing and water-soluble base to be used should be 0.1 to 60 wt%, or desirably 1 to 50 wt%, against the water-absorbing and water-insoluble base.

In this invention, at least 90 wt% particles of the powdery composition have an effective diameter of 10 to 250 μm. By controlling the particle diameter of the particles of the powdery composition in the abovementioned range, it becomes possible to have the powdery composition diffused widely over the nasal mucous membrane when intranasally administered, to make the powdery composition stay longer at the place where it has adhered, and to facilitate the efficient intranasal administration upon pernasal spraying of the powdery composition through the nostril.

When a powdery composition which contains more than 10 wt% particles having an effective diameter of less than 10 μm is nasally administered by spraying, more particles will go further into the lungs or escape from the nostrils. Also, such a powdery composition has difficulty in maintaining its effective drug concentration at a high level. On the other hand, when a powdery composition which contains more than 10 wt% particles having an effective diameter of more than 250 μm is intranasally administered, part of the particles on the nasal mucous membrane will readily separate from there, thus undesirably making its efficacy less stayable. It is especially desirable to control the powdery composition to have more than 90 wt% its particles measuring 20 to 150 μm in effective diameter.

The powdery composition of this invention may have any of the structures such as one in which the water-absorbing and water-insoluble base and polypeptide or its derivative form independent particles, one in which the polypeptide or its derivative particles are adhered to the surface of the water-absorbing and water-insoluble base particle, one in which the polypeptide or its derivative particles are dispersed in the water-absorbing and water-insoluble base particle, both forming separate phases of their own, or one in which the polypeptide or its derivative particles are closely dispersed in the water-absorbing and water-insoluble base particle, thus forming uniform dispersion.

The powdery composition of this invention, which has a structure in which the water-absorbing and water-insoluble base and polypeptide or its derivative form independent particles or the polypeptide or its derivative particles are adhered to the surface of the water-absorbing and water-insoluble base particles, can be prepared by first adding polypeptide or its derivative to a water-absorbing and water-insoluble base, then mixing them by a mechanical process, and finally filtering them to obtain the desired composition with more than 90 wt% of its particles measuring 10 to 250 μm in effective diameter.

In case where a water-absorbing and water-soluble base is used in combination with a water-absorbing and water-insoluble base, both bases may be mixed together simultaneously with the polypeptide or its derivatives in the mechanical mixing process.

The powdery composition of this invention, which has a structure in which the polypeptide or its derivative particles are dispersed in the water-absorbing and water-insoluble base particles, both forming separate phases of their own, or the polypeptide or its derivative particles are closely dispersed in the water-absorbing and water-insoluble base particles, thus forming a uniform dispersion, can be obtained by following the procedure mentioned below. It is prepared by firstly mixing the polypeptide or its derivative with a water-absorbing and water-insoluble base by mechanical means, then compacting the obtained mixture under pressure, further pulverizing the compacted mixture, and finally filtering the resulting pulverulence to obtain the desired composition with more than 90 wt% its particles measuring 10 to 250 μm in effective diameter. The powdery composition can also be obtained by thoroughly mixing the polypeptide or its derivative with a water-absorbing and water-insoluble base in water to make a thin smooth pasty mixture, drying and pulverizing the mixture according to ordinary methods, and finally passing the pulverized composition through a sieve.

In the case where a water-absorbing and water-soluble base is to be used jointly, it may be admixed with the polypeptide or its derivative and a water-absorbing and water-insoluble base in the mechanical mixing process, followed by the abovementioned processes of compacting, etc., or a water-absorbing and water-soluble base may be introduced into the process wherein the polypeptide or its derivative is mixed with a water-absorbing and water-insoluble base in the presence of water.

There is also another method of obtaining a powdery composition by joint use of a water-absorbing and water-soluble base, wherein a water-absorbing and water-soluble base is added to the polypeptide or its derivative in the process in which the polypeptide or its derivative is to be freeze-dried, thus both components being freeze-dried simultaneously as mentioned above.

In order to improve the properties, appearance or odor of the powdery pharmaceutical composition of this invention, it may, if desired, contain any of the known additives such as coloring agents, preservatives, antiseptics, corrigents, etc. As the coloring agents, there are, for instance, β-carotene, Red No. 2 and Blue No. 1; as the preservatives, there are for instance stearic acid, ascorbyl stearate and ascorbic acid; as the antiseptics, there are for instance p-hydroxybenzoate, phenol and chlorobutanol, and as the corrigents, there are for instance menthol and citrus perfume.

The powdery pharmaceutical composition of this invention can be directly used as a powder for a unit dosage form.

As the desirable form for administration, the powder can be filled in capsules such as hard gelatin capsules.

As the method of pernasally applying the powdery preparation to the nasal cavity by spraying, there is, for instance, a method in which a capsule filled with the powdery preparation is placed in a sprayer, which is exclusively designed for this purpose and equipped with a needle, then the capsule is pierced with the needle to have minute holes on both the top and bottom, and thereafter jets of powder are sent into the nasal cavity by means of ballooning, etc.

The following examples illustrate the present invention more specifically; however, it should be understood that these examples are given to explain the invention and not to limit the scope of the invention.

Example 1

(i) Powdery pharmaceutical compositions for pernasal administration were obtained as follows:

(a) 400 mg of water-soluble insulin powder, which was obtained by freeze-drying a solution prepared by dissolving insulin in 0.1N-HCl aqueous solution and further adding pure water thereto, and 3,600 mg of crystalline cellulose were placed in a mixer and mixed thoroughly to obtain a uniform powdery composition, at least 90 wt% of the particles of which had a particle diameter of 75 to 149 μm. Thus obtained powdery composition had insulin activity of 2.55 units/mg.

(b) 10 mg of insulin (25.5 units/mg) was dissolved in 0.2 ml of 0.1 N hydrochloric acid. 200 ml of water was added thereto to give an aqueous solution of insulin and 40 mg of polyacrylic acid (Carbopol 934) was dissolved therein. About 30 ml of an aqueous solution of 0.01 N sodium hydroxide was added to the solution to adjust it to pH 7.4. The solution was then freeze-dried to give a neutral and uniform powdery composition (I) wth 5.1 units/mg of insulin, comprising insulin and sodium polyacrylate (neutral Carbopol 934).

Then, 50 mg of the thus obtained powdery composition (I) and 50 mg of crystalline cellulose were put in a mortar and mixed thoroughly to obtain a uniform powdery composition (II), at least 90 wt% of the particles of which had a particle diameter of 75 to 149 μm. The obtained powdery composition (II) had insulin activity of 2.55 units/mg.

(c) The powdery compositions containing insulin prepared in the foregoing (a) and (b) were respectively filled in capsules to obtain insulin preparations for human pernasal administration.

(ii) The following comparative compositions were obtained to compare with the compositions of this invention.

(d) 700 mg of water-soluble insulin powder (25.5 units/mg), which was obtained by once dissolving insulin, then followed by freeze-drying, and 6,300 mg of lactose were placed in a mixer and mixed well to give a uniform powdery composition, at least 90 wt% of the particles of which had a particle diameter of 75 to 149 μm. Thus obtained powdery composition contained 2.55 units/mg of insulin.

(e) 400 mg of water-soluble insulin powder (25.5 units/mg), which was obtained by once dissolving insulin and then freeze-drying the solution, and 3,600 mg of hydroxypropyl cellulose were placed in a mixer and mixed thoroughly to give a uniform powdery composition, at least 90 wt% of the particles of which had a particle diameter of 75 to 149 μm. The powdery composition thus obtained contained 2.55 units/mg of insulin.

Example 2

(Experiment of nasal administration of powdery insulin preparation in dogs)

3 units/kg of the respective powdery compositions of insulin prepared in Example 1, (a), (b), (d), and (e) were administered intranasally to male Beagle dogs (weighing 9.4 to 12.6 kg) which were anesthetized by intravenous injection of nembutal (containing 50 mg/ml of pentobarbital sodium) in 25 mg/kg doses. The administration of the powdery composition of insulin was carried out by spraying it into the nasal cavity with a double balloon through a polyethylene tube (about 2 mm in diameter) inserted about 3 cm into the nostril, and blood was withdrawn from the foreleg vein as time passed after the administration. The glucose level of plasma was measured by o-toluidine (Clinical Chemistry, *8*, 215 (1962)). Fig. 1 shows the decrease (%) of the plasma glucose levels from that before administration of insulin. The values shown in Fig. 1 are the average values of four Beagle dogs. The change in plasma glucose levels after the nasal administration of 5 units/10 ul/kg, by use of a micropipette, of an aqueous suspension of original insulin powder is shown by a broken line in Fig. 1 for the sake of comparison. In Fig. 1, (1) indicates the case where crystalline cellulose was used as the base (Example 1, (a)), (2) the case where freeze-dried insulin-sodium polyacrylate and crystalline cellulose were used (Example 1, (b)), (3) the case were lactose was used as the base (Example 1, (d)), and (4) the case where hydroxypropyl cellulose was used as the base (Example 1, (e)) respectively.

It is clear from Fig. 1 that the compositions in which crystalline cellulose is used show a highly efficient absorption of insulin and that the composition in which sodium polyacrylate is used in combination with crystalline cellulose show a highly efficient absorption of insulin as well as a sustained release effect.

Example 3

(i) 100 mg of porcine insulin was dissolved in 1 ml of 0.1 N hydrochloric acid, to which 40 ml of distilled water was added to obtain an insulin solution. The obtained solution was freeze-dried to give water-

soluble insulin powder (26.3 units/mg). The following powdery composition (a) of this invention was obtained from this insulin powder.

(a) 20 mg of the water-soluble insulin powder obtained in the above (26.3 units/mg) and 140 mg of crystalline cellulose were weighed into a mortar and mixed thoroughly to obtain a uniform powdery composition. The powdery composition thus obtained contained about 3.3 units/mg of insulin.

(ii) With the purpose of comparing with the preceding powdery composition (a) of this invention, the following comparative powdery compositions (b) and (c) were prepared from the aforementioned insulin powder.

(b) 15 mg of the water-soluble insulin powder (26.3 units/mg) and 105 mg of lactose were put in a mortar and mixed well to obtain a uniform powdery composition. The obtained powdery composition contained 3.3 units/mg of insulin.

(c) 20 mg of the water-soluble insulin powder (26.3 units/mg) and 140 mg of hydroxypropyl cellulose were placed in a mortar and mixed thoroughly to obtain a uniform powdery composition. The powdery composition thus obtained contained about 3.3 units/mg of insulin.

Example 4

(Experiment of nasal administration of powdery insulin preparation in rabbit.)

10 units/head of the respective powdery composition of insulin prepared in Example 3, (a) to (c), were administered intranasally to white native male rabbits (weighing 3.0 to 3.5 kg). Blood was withdrawn from the ear vein 10 minutes, 20 minutes, 30 minutes, and 60 minutes after administration and also before administration. The administration of the powdery composition of insulin was carried out by use of a sprayer specially modified for animal use while the rabbits were lightly anesthetized by ether or not. The insulin level of the serum was determined according to radioimmunoassay. The result is shown in Fig. 2 in which the values are the average values of three rabbits. Also, the result, which was obtained from the experiment conducted likewise with the nasal administration of 10 units/50 μl/head, by use of a micropipette, of an aqueous suspension of the original insulin powder, is shown by a broken line in Fig. 2 for the sake of comparison.

In Fig. 2, (1) indicates the case where crystalline cellulose was used as the base (Example 3, (a)), (2) the case where lactose was used as the base (Example 3, (b)), and (3) the case where hydroxypropyl cellulose was used as the base (Example 3, (c)) respectively.

It is clear from Table 2 that the composition of this invention shows a highly efficient absorption of insulin.

Example 5

2,000 mg of crystalline cellulose and 0.5 mg of freeze-dried [$ASU^{1.7}$]-eel calcitonin (4,000 MRC units/mg) were placed in a mortar and mixed most thoroughly to obtain a uniform powdery composition. The obtained powdery composition contained about 1 MRC unit/mg of [$ASU^{1.7}$]-eel calcitonin. The powdery composition was filled in the prescribed capsules with the capsule filler, each capsule containing 10 to 50 mg, to obtain a preparation for human nasal application.

Also, exampes of preparation of calcitonin powdery compositions for animal experiment use are given in the following (a) and (b).

(a) 200 mg of crystalline cellulose and 0.3 mg of freeze-dried [$ASU^{1.7}$]-eel calcitonin (4,000 MRC units/mg) were put in a mortar and mixed thoroughly to obtain a uniform powdery composition. The obtained powdery composition contained 5.99 MRC units of [$ASU^{1.7}$]-eel calcitonin.

(b) 100 mg of crystalline cellulose and 0.3 mg of freeze-dried salmon calcitonin (2,000 MRC uits/mg) were placed in a mortar and mixed well to obtain a uniform powdery composition. The obtained powdery composition contained 5.98 MRC units/mg of salmon calcitonin.

Example 6

(Experiment of nasal administration of powder calcitonin preparations in rabbits.)

6 MRC units/kg of the respective powdery compositions of calcitonin prepared in Example 5, (a) and (b), were administered intranasally to white native male rabbits (weighing 2.5 to 3.0 kg). Blood was withdrawn from their ear veins before administration and 1 hour, 2 hours, 4 hours, and 6 hours after

administration. The administration of the powdery composition was carried out in the same way as the second animal experiment made in Example 4. The concentration of serum calcium before and after administration was measured to study the absorbability of calcitonin through the nasal mucous membrane. The measurement of serum calcium levels was made with the use of a calcium measurement kit (IATRON Co.). The result is shown in Table 1 in which the decrease of serum calcium levels as compared with serum calcium levels obtained before administration of powdery preparation of calcitonin is shown in percentages. The levels described in the table are the average values of three rabbits.

As control, 60 MRC units/50 μ/kg of almost neutral aqueous solution of [ASU^{1,7}]-eel calcitonin was nasally administered and the result is shown in Table 1.

Table 1

	Powdery preparation		Decrease of serum calcium as compared with preadministration (%)			
	Base	Calcitonin dosage	1 hour	2 hrs	3 hrs	4 hrs
Preparation of this invention	Crystalline cellulose	[ASU^{1,7}]-eel calcitonin 6 MRC units/kg	10.3	9.1	2.2	0.3
	Crystalline cellulose	Salmon calcitonin 6 MRC units/kg	9.6	7.5	0.7	-0.3
Control	Water	[ASU^{1,7}]-eel calcitonin 6 MRC units/kg	2.7	1.7	0.0	0.7

Example 7

490 mg of crystalline cellulose and 10 mg of freeze-dried vasopressin (70 to 100 units/mg) were put in a mortar and mixed thoroughly to give a uniform powdery composition. The obtained powdery composition contained 1.4 to 2.0 units/mg of vasopressin.

The powdery composition thus obtained was then encapsulated according to the prescription to give a preparation for human nasal application.

Example 8

990 mg of crystalline cellulose was weighed into a mortar and 10 mg of freeze-dried luteinizing hormone releasing hormone was added thereto. They were mixed thoroughly to obtain a uniform powdery composition. The obtained powdery composition contained 10 μg/mg of luteinizing hormone releasing hormone and the powdery composition was then filled in the prescribed capsules to give a preparation for human nasal application.

Example 9

950 mg of crystalline cellulose was placed in a mortar, to which 50 mg of interferon (10^5 units/mg), which had been freeze-dried together with human serum albumin, was added. They were mixed thoroughly to obtain a uniform powdery composition. The powdery composition thus obtained contained 5,000 units/mg of interferon and was encapsulated according to the prescription to obtain a preparation for human nasal application.

Example 10

2,000 mg of crystalline cellulose and 1 mg of freeze-dried desmopressin acetate were mixed thoroughly in a mortar to obtain a uniform powdery composition. The obtained powdery composition contained 0.5 μg/mg of desmopressin acetate. This composition was encapsulated according to the prescription to give a preparation for human nasal application.

Example 11

2,000 mg of crystalline cellulose and 0.5 mg (4,000 MRC units/mg) of freeze-dried [ASU^{1,7}]-eel calcitonin or 1.0 mg (2,000 MRC units/mg) of salmon calcitonin were placed in a mortar and mixed well to obtain a uniform powdery composition. The obtained powdery composition contained about 1 MRC unit/mg of [ASU^{1,7}]-eel calcitonin or salmon calcitonin.

10 to 50 mg of the powdery composition these obtained was then encapsulated according to the prescription to give a preparation for human nasal application.

Example 12

199 mg of hydroxypropylcellulose and 1 mg (2,000 MRC units/mg of salmon calcitonin were dissolved in 50 ml of water. The solution was freeze-dried to give a uniform powdery composition with salmon calcitonin activity of 10 MRC units/mg, comprising salmon calcitonin and hydroxypropylcellulose.

100 mg of the powdery composition and 900 mg of crystalline cellulose were placed in a mortar and mixed thoroughly to obtain a uniform powdery composition, at least 90 wt% of the particles of which had a particle diameter of 10 to 250 μm.

Thus obtained powdery composition contained 1 MRC unit/mg of the salmon calcitonin. 10 to 50 mg of the powdery composition thus obtained was then encapsulated according to the prescription to give a preparation for human nasal application.

Example 13

499 mg of hydroxypropylcellulose and 1 mg (4,000 MRS units/mg) of [ASU^{1,7}]-eel calciton were mixed.

200 mg of of the powdery composition and 800 mg of crystalline cellulose were placed in a mortar and mixed thoroughly to obtain a powdery composition, at least 90 wt% of the particles of which had a particle diameter of 10 to 250 μm.

Thus obtained powdery composition contained 1.6 MRC units/mg of [ASU^{1,7}]-eel calciton. 10 to 50 mg of the powdery composition thus obtained was then encapsulated according to the prescription to give a preparation for human nasal application.

Example 14

One mg of formalin-detoxificated Partussis toxin (PT and 1 mg of formalin-treated filamentous hemagglutinin (F-HA), those were components of a cellular pertussis vaccine developed recently in Japan) and 1,000 mg of crystalline cellulose were placed in a mortar and mixed well to obtain a uniform powdery composition.

The obtained powdery composition contained about totally 2 μg/mg of both components.

10 to 25 mg of this composition was then encapsulated according to the prescription to give a preparation for human nasal application.

Example 15

800 mg of hydroxypropylcellulose and 200 mg of powdery freeze-dried influenza HA vaccine were placed in a mortar and mixed well to obtain a uniform powdery composition. The powdery composition contained about 200 μ/mg of freeze-dried influenza HA vaccine. 50 mg of the powdery composition and 950 mg of crystalline cellulose were placed in a mortar and mixed well to give a uniform powdery composition, at least 90 wt% of the particles of which had a particle diameter of 10 to 150 μm. Thus obtained powdery composition contained 10 μm/mg of freeze-dried influenza HA vaccine. 10 to 30 mg of powdery composition thus obtained was then encapsulated according to the prescription to give a preparation for human nasal application.

Claims

1. A powdery pharmaceutical composition adapted for nasal administration comprising: (i) a physiologically active polypeptide or its derivative; (ii) a water-absorbing and water-insoluble base selected from celluloses, starches and cross-linked vinyl polymers; and (iii) obtionally a water-absorbing and water-soluble base, said water-absorbing and water-soluble base being present in an amount of 0.1 to 60

wt%, against the water-absorbing and water-insoluble base; wherein at least 90 wt% of the particles of said composition have an effective diameter ranging from 10 to 250 µm, and wherein said particles do not disintegrate on spraying, provided that the composition does not comprise a mixture of bacitracin and starch.

2. A powdery pharmaceutical composition according to Claim 1, wherein said base is a water-absorbing and water-insoluble cellulose.

3. A powdery pharmaceutical composition according to Claim 2, wherein said water-absorbing and water-insoluble cellulose is crystalline cellulose, α-cellulose, or cross-linked sodium carboxymethyl cellulose.

4. A powdery pharmaceutical composition according to Claim 3, wherein said water-absorbing and water-insoluble cellulose is crystalline cellulose.

5. A powdery pharmaceutical composition according to claim 1 wherein said base is a water-absorbing and water-insoluble cross-linked vinyl polymer.

6. A powdery pharmaceutical composition according to claim 5, wherein said water-absorbing and water-insoluble cross-linked vinyl polymer is cross-linked polyvinylpyrrolidone or cross-linked carboxy vinyl polymer.

7. A powdery pharmaceutical composition according to any one of claims 1 to 6, wherein said water-absorbing and water-soluble base is a lower alkyl ether of cellulose, a polyacrylate, polyethyleneglycol or polyvinyl pyrrolidone.

8. A powdery pharmaceutical composition according to any one of claims 1 to 7, wherein said physiologically active polypeptide or its derivative is a polypeptide or its derivative with a molecular weight of 1,000 to 300,000.

9. A powdery pharmaceutical composition according to any one of claims 1 to 8, wherein said physiologically active polypeptide or its derivative is a water-soluble polypeptide or its derivative.

10. A powdery pharmaceutical composition according to any one of claims 1 to 9, wherein said physiologically active polypeptide or its derivative is a peptide hormone, a physiologically active protein, an enzyme protein, or a vaccine.

11. A powdery pharmaceutical composition according to Claim 10, wherein said physiologically active polypeptide or its derivative is a peptide hormone.

12. A powdery pharmaceutical composition according to Claim 11, wherein said peptide hormone is calcitonin, insulin, luteinizing hormone releasing hormone, desmopressin, vasopressin or oxytocin.

13. A powdery pharmaceutical composition according to Claim 10, wherein said physiologically active polypeptide or its derivative is a vaccine.

14. A powdery pharmaceutical composition according to Claim 13, wherein said vaccine is influenza vaccine or pertussis vaccine.

15. A powdery pharmaceutical composition according to Claim 10, wherein said physiologically active polypeptide or its derivative is a physiologically active protein.

16. A powdery pharmaceutical composition according to Claim 15, wherein said physiologically active protein is interferon.

Patentansprüche

1. Pulverförmiges pharmazeutisches Mittel, angepaßt für eine nasale Verabreichung, umfassend: (i) ein physiologisch aktives Polypeptid oder sein Derivat, (ii) eine wasserabsorbierende und wasserunlösliche

Grundlage, ausgewählt aus Zellulosen, Stärken und vernetzten Vinylpolymeren; und (iii) gegebenenfalls eine wasserabsorbierende und wasserlösliche Grundlage, wobei die wasserabsorbierende und wasserlösliche Grundlage in einer Menge von 0,1 bis 60 Gew.-%, bezogen auf die wasserabsorbierende und wasserunlösliche Grundlage, zugegen ist; wobei wenigstens 90 Gew.-% der Teilchen des Mittels einen wirksamen Durchmesser von 10 bis 250 µm besitzen, und wobei die Teilchen beim Sprühen nicht zerfallen, mit der Maßgabe, daß das Mittel kein Gemisch aus Bacitracin und Stärke umfaßt.

2. Pulverförmiges pharmazeutisches Mittel nach Anspruch 1, wobei die Grundlage eine wasserabsorbierende und wasserunlösliche Zellulose ist.

3. Pulverförmiges pharmazeutisches Mittel nach Anspruch 2, wobei die wasserabsorbierende und wasserunlösliche Zellulose eine kristalline Zellulose, alpha-Zellulose oder eine vernetzte Natriumcarboxymethylzellulose ist.

4. Pulverförmiges pharmazeutisches Mittel nach Anspruch 3, wobei die wasserabsorbierende und wasserunlösliche Zellulose kristalline Zellulose ist.

5. Pulverförmiges pharmazeutisches Mittel nach Anspruch 1, wobei die Grundlage ein wasserabsorbierendes und wasserunlösliches vernetztes Vinylpolymeres ist.

6. Pulverförmiges pharmazeutisches Mittel nach Anspruch 5, wobei das wasserabsorbierende und wasserunlösliche vernetzte Vinylpolymere vernetztes Polyvinylpyrrolidon oder vernetztes Carboxyvinylpolymeres ist.

7. Pulverförmiges pharmazeutisches Mittel nach einem der Ansprüche 1 bis 6, wobei die wasserabsorbierende und wasserlösliche Grundlage ein niederer Alkylether von Zellulose, ein Polyacrylat, Polyethylenglykol oder Polyvinylpyrrolidon ist.

8. Pulverförmiges pharmazeutisches Mittel nach einem der Ansprüche 1 bis 7, wobei das physiologisch aktive Polypeptid oder sein Derivat ein Polypeptid oder sein Derivat mit einem Molekulargewicht von 1000 bis 300000 ist.

9. Pulverförmiges pharmazeutisches Mittel nach einem der Ansprüche 1 bis 8, wobei das physiologisch aktive Polypeptid oder sein Derivat ein wasserlösliches Polypeptid oder sein Derivat ist.

10. Pulverförmiges pharmazeutisches Mittel nach einem der Ansprüche 1 bis 9, wobei das physiologisch aktive Polypeptid oder sein Derivat ein Peptidhormon, ein physiologisch aktives Protein, ein Enzymprotein oder ein Vakzin ist.

11. Pulverförmiges pharmazeutisches Mittel nach Anspruch 10, wobei das physiologisch aktive Polypeptid oder sein Derivat ein Peptidhormon ist.

12. Pulverförmiges pharmazeutisches Mittel nach Anspruch 11, wobei das Peptidhormon Calcitonin, Insulin, ein luteinisierendes Hormon, freisetzendes Hormon, Desmopressin, Vasopressin oder Oxytocin ist.

13. Pulverförmiges pharmazeutisches Mittel nach Anspruch 10, wobei das physiologisch aktive Polypeptid oder sein Derivat ein Vakzin ist.

14. Pulverförmiges pharmazeutisches Mittel nach Anspruch 13, wobei das Vakzin Grippevakzin oder Keuchhustenvakzin ist.

15. Pulverförmiges pharmazeutisches Mittel nach Anspruch 10, wobei das physiologisch aktive Polypeptid oder sein Derivat ein physiologisch aktives Protein ist.

16. Pulverförmiges pharmazeutisches Mittel nach Anspruch 15, wobei das physiologisch aktive Protein Interferon ist.

Revendications

1. Composition pharmaceutique pulvérulente appropriée pour une administration nasale, comprenant : (i) un polypeptide physiologiquement actif, ou son dérivé, (ii) une base, insoluble dans l'eau et capable d'absorber de l'eau choisie parmi les celluloses, les amidons ou fécules et les polymères vinyliques réticulés ; et (iii) éventuellement une base hydrosoluble et capable d'absorber de l'eau, ladite base hydrosoluble et capable d'absorber de l'eau étant présente en une quantité allant de 0,1 à 60% en poids, par rapport à la base insoluble dans l'eau et capable d'absorber de l'eau ; dans laquelle, au moins 90% en poids des particules de ladite composition possèdent un diamètre effectif compris entre 10 et 250 µm et dans laquelle lesdites particules ne se désagrègent pas lors de l'application par pulvérisation, à la condition que la composition ne comprenne pas un mélange de bacitracine et d'amidon ou fécule.

2. Composition pharmaceutique pulvérulente selon la revendication 1, dans laquelle ladite base est une cellulose insoluble dans l'eau et capable d'absorber de l'eau.

3. Composition pharmaceutique pulvérulente selon la revendication 2, dans laquelle ladite cellulose insoluble dans l'eau et capable d'absorber de l'eau est de la cellulose cristalline, de l'α-cellulose, ou de la carboxyméthyl cellulose sodique réticulée.

4. Composition pharmaceutique pulvérulente selon la revendication 3, dans laquelle ladite cellulose insoluble dans l'eau et capable d'absorber de l'eau est de la cellulose cristalline.

5. Composition pharmaceutique pulvérulente selon la revendication 1, dans laquelle ladite base est un polymère vinylique réticulé insoluble dans l'eau et capable d'absorber de l'eau.

6. Composition pharmaceutique pulvérulente selon la revendication 5, dans laquelle ledit polymère vinylique réticulé, insoluble dans l'eau et capable d'absorber de l'eau, est une polyvinylpyrrolidone réticulée ou un polymère carboxy vinylique réticulé.

7. Composition pharmaceutique pulvérulente selon l'une quelconque des revendications 1 à 6, dans laquelle ladite base hydrosoluble et capable d'absorber de l'eau est un éther alkylique inférieur de la cellulose, un polyacrylate, un polyéthylène glycol ou une polyvinyl pyrrolidone.

8. Composition pharmaceutique pulvérulente selon l'une quelconque des revendications 1 à 7, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est un polypeptide, ou son dérivé, ayant un poids moléculaire de 1 000 à 300 000.

9. Composition pharmaceutique pulvérulente selon l'une quelconque des revendications 1 à 8, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est un polypeptide hydrosoluble ou son dérivé.

10. Composition pharmaceutique pulvérulente selon l'une quelconque des revendications 1 à 9, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est une hormone peptidique, une protéine physiologiquement active, une protéine enzymatique ou un vaccin.

11. Composition pharmaceutique pulvérulente selon la revendication 10, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est une hormone peptidique.

12. Composition pharmaceutique pulvérulente selon la revendication 11, dans laquelle ladite hormone peptidique est la calcitonine, l'insuline, une hormone libérant l'hormone de lutéinisation, la desmopressine, la vasopressine ou l'oxytocine.

13. Composition pharmaceutique pulvérulente selon la revendication 10, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est un vaccin.

14. Composition pharmaceutique pulvérulente selon la revendication 13, dans laquelle ledit vaccin est un vaccin contre la grippe ou un vaccin contre la coqueluche.

15. Composition pharmaceutique pulvérulente selon la revendication 10, dans laquelle ledit polypeptide physiologiquement actif, ou son dérivé, est une protéine physiologiquement active.

16. Composition pharmaceutique pulvérulente selon la revendication 15, dans laquelle ladite protéine physiologiquement active est l'interféron.

FIG. 1

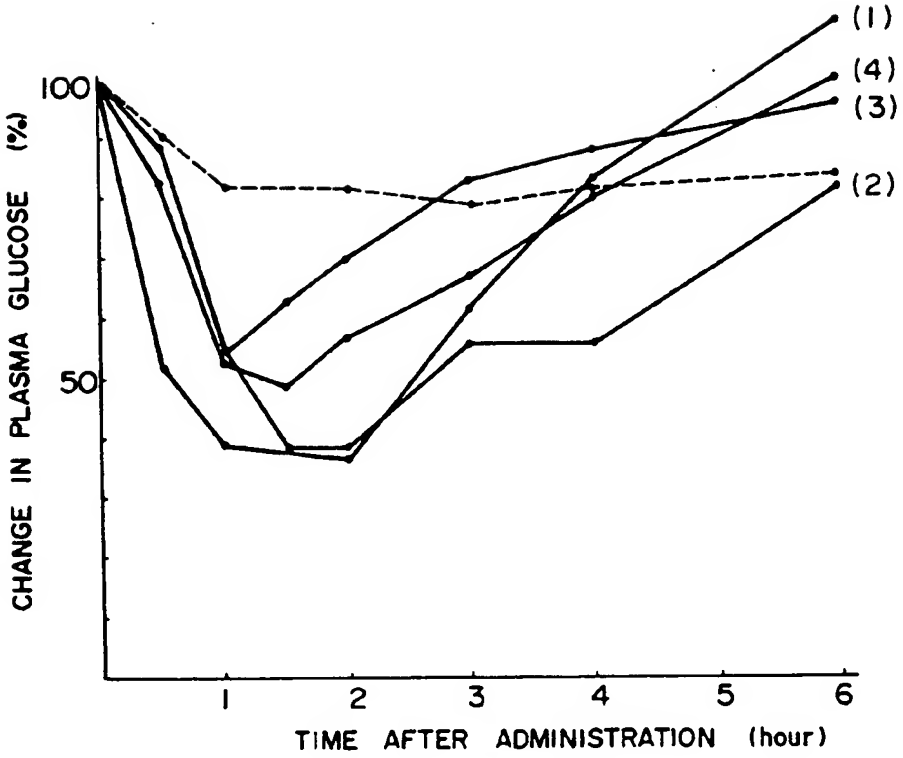
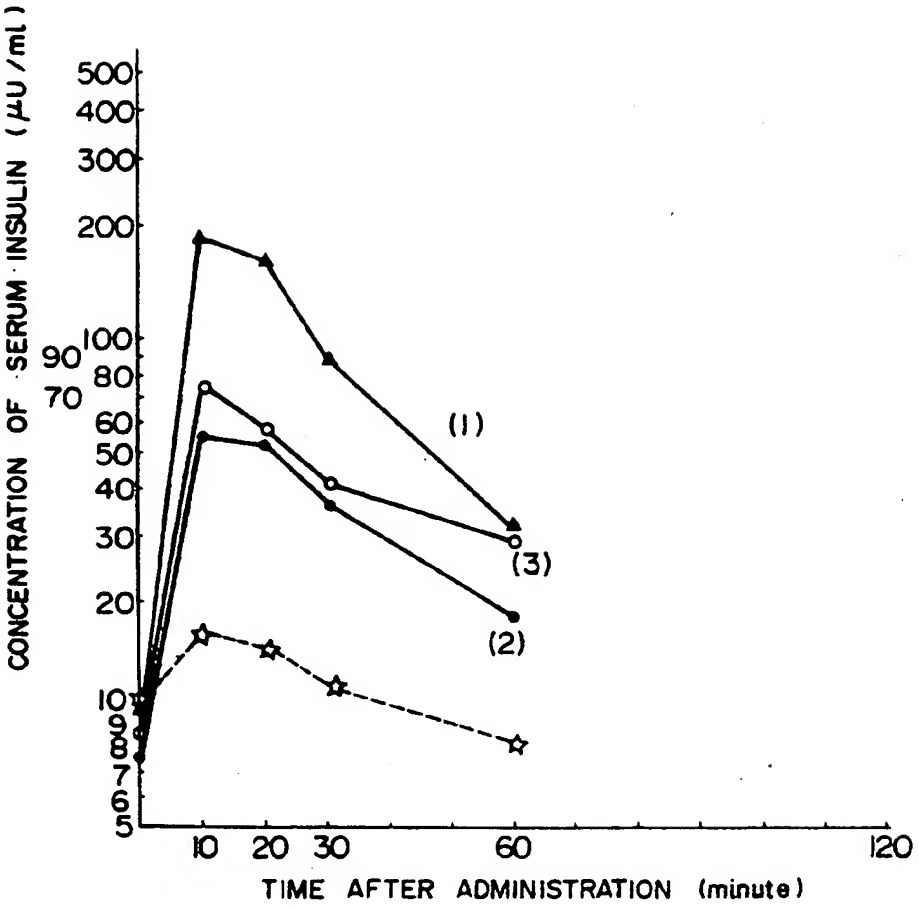

(1)
(4)
(3)
(2)
100
50
CHANGE IN PLASMA GLUCOSE (%)
1
2
3
4
5
6
TIME AFTER ADMINISTRATION (hour)

FIG. 2


CONCENTRATION OF SERUM INSULIN (μU/ml)
500
400
300
200
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
(1)
(2)
(3)
10
20
30
60
120
TIME AFTER ADMINISTRATION (minute)